

*A pilot randomised controlled trial of a programme of psychosocial interventions (resettle) for high risk personality disordered offenders*

Article

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1 **Mismatched prenatal and postnatal maternal depressive symptoms and child**  
2 **behaviours: a sex-dependent role for *NR3C1* DNA methylation in the Wirral Child**  
3 **Health and Development Study**

4  
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22 **Abstract**

23 Evolutionary hypotheses predict that male fetuses are more vulnerable to poor maternal  
24 conditions (Sex-biased Maternal Investment), but female fetuses are at greater risk of  
25 glucocorticoid-mediated disorders where there is a mismatch between fetal and postnatal  
26 environments (Predictive Adaptive Response). Self-reported prenatal and postnatal depression  
27 and maternal report of child anxious-depressed symptoms at 2.5, 3.5 and 5.0 years were  
28 obtained from an ‘extensive’ sample of first-time mothers (N=794). Salivary *NR3C1* 1-F  
29 promoter methylation was assayed at 14 months in an ‘intensive’ subsample (n=176), stratified  
30 by psychosocial risk. Generalised structural equation models were fitted and estimated by  
31 maximum likelihood to allow inclusion of participants from both intensive and extensive  
32 samples. Postnatal depression was associated with *NR3C1* methylation and anxious-depressed  
33 symptoms in daughters of mothers with low prenatal depression (prenatal-postnatal depression  
34 interaction for methylation,  $p < .001$ ; for child symptoms,  $p = .011$ ). In girls, *NR3C1* methylation  
35 mediated the association between maternal depression and child anxious-depressed symptoms.  
36 Effects were greater in girls than boys: the test of sex differences in the effect of the prenatal-  
37 postnatal depression interaction on both outcomes gave  $\chi^2(2) = 5.95$  ( $p = .051$ ). This is the first  
38 study to show in humans that epigenetic and early behavioural outcomes may arise through  
39 different mechanisms in males and females.

40

41 Key Words: maternal depression: *NR3C1* methylation; child anxiety-depression: sex  
42 differences: parental reproductive investment: epidemiological sampling: mediation:  
43 longitudinal design

## 44 **Introduction**

45 The ‘fetal origins’ hypothesis was first proposed to account for associations between low birth  
46 weight and obesity, cardiovascular disease, and Type II diabetes in middle and old age [1].  
47 According to this hypothesis, low birth weight reflects evolved adaptive mechanisms that  
48 confer advantages later in life where food is scarce, but create risk in the presence of high  
49 calorie diets, common in industrialised societies. Far from being a mechanism specific to  
50 nutrition in humans, adaptations prior to birth that anticipate later environments are found  
51 across species, possibly reflecting a conserved ‘Predictive Adaptive Response’ (PAR)  
52 mechanism [2, 3]. According to the PAR hypothesis, matched prenatal and postnatal conditions  
53 will be associated with good outcomes, while mismatching creates risks for poor outcomes. In  
54 relation to effects on psychiatric disorders, many studies have reported that anxiety, depression  
55 and behavioural symptoms in children are predicted by prenatal stressors, maternal depression  
56 and anxiety, and by low birth weight [4 - 9]. We have previously reported that the association  
57 between prenatal anxiety and child emotional and behavioural outcomes is seen only in the  
58 presence of low maternal stroking, consistent with animal studies of the protective effects of  
59 postnatal tactile stimulation [8]. We went on to show that mismatched prenatal – postnatal  
60 maternal anxiety is associated with elevated child irritability at age 7 years, only in the presence  
61 of low maternal stroking REF, consistent with a mismatch effect creating vulnerability that is  
62 modified by early tactile stimulation.

63 Fetal adaptations may additionally vary by sex of the fetus. According to the Trivers-  
64 Willard (T-W) hypothesis, if maternal health during pregnancy predicts later reproductive  
65 fitness in the offspring, then a male predominance of births will be favoured when maternal  
66 conditions are good, because healthy males compete successfully for females. By contrast,  
67 when maternal conditions are poor, the sex ratio will be reversed, both to avoid bearing males  
68 who compete less successfully for females, but also because, compared to females, health

69 outcomes for mothers following male births are poorer [10]. Although this hypothesis has been  
70 subject to challenges and modifications [11], the central idea that reproductive strategies  
71 associated with poor maternal conditions involve sacrifice of males and protection of females  
72 has received substantial support. It is also consistent with well documented observations that  
73 male fetuses are more vulnerable to threats such as preterm birth and are more likely to suffer  
74 neurodevelopmental consequences of fetal insults [12]. This hypothesis would appear to  
75 predict better outcomes for females following poor maternal conditions. However, if this  
76 protective effect in females arises from advantages conferred by fetal anticipation of matched  
77 environments (PAR hypothesis), mismatches between maternal conditions during pregnancy  
78 and the postnatal environment will create vulnerability. Combining the T-W and PAR  
79 hypotheses leads to the prediction that the effects of prenatal risks will operate differently in  
80 males and females. In females, vulnerability will be generated by particular combinations of  
81 prenatal and postnatal risks, while in males, poor outcomes will arise incrementally from  
82 degree of prenatal risk. In the only human study we are aware of to have examined the  
83 combined effects predicted by the T-W and PAR hypotheses, matched environments indexed  
84 by prenatal and postnatal depression (low-low and high-high) were associated with better  
85 cognitive and motor outcomes over the first year of life than mismatched prenatal and postnatal  
86 depression, and this effect was seen in females only [13]. However, many studies have reported  
87 sex differences in developmental outcomes in relation to prenatal risks, without examining for  
88 the interplay with postnatal environments. Sex differences in fetal responses to stress [14], and  
89 in later emotional and behavioural problems following maternal anxiety or depression during  
90 pregnancy and low birth weight [4, 7, 8, 15, 16], have been identified.

91 In animal models, prenatal and postnatal stress cause long-term elevations in  
92 hypothalamic pituitary axis (HPA) reactivity and anxiety-like behaviours. This is mediated via  
93 reduced glucocorticoid receptor (GR) gene *NR3C1* expression, particularly in the hippocampus

94 which impairs HPA axis feedback mechanisms [17]. The epigenetic process of DNA  
95 methylation involves the addition of methyl groups to CpG dinucleotides in gene regulatory  
96 regions that are associated with repressed gene expression. Animal findings of the epigenetic  
97 effects of early life stress have been translated to humans in a study reporting elevated *NR3CI*  
98 1-F promoter methylation and reduced *NR3CI* expression in post-mortem hippocampal tissue  
99 of people who have committed suicide and who were abused during childhood, when compared  
100 to non-abused [18]. Other studies using peripheral DNA from blood or saliva of infants and  
101 adolescents have shown increased levels of *NR3CI* methylation associated with prenatal and  
102 childhood adversities [19, 20, 21]. Several clinical studies examining leukocytes have reported  
103 elevated methylation of the homologous human *NR3CI* 1-F promoter (homologous to the rat  
104 1-7 promoter) at a specific CpG (CpG unit 22,23, Figure 1) associated with prenatal maternal  
105 depression [19, 22-24] and childhood stress [25]. Studies in humans also find associations  
106 between prenatal anxiety and postnatal depression in mothers, and adolescent depressive  
107 symptoms mediated via HPA axis dysregulation [26, 27], consistent with the role of HPA axis  
108 dysregulation in adolescent depression [28]. Higher *NR3CI* methylation levels, hypothesised  
109 to contribute to reduced *NR3CI* expression (18), have been associated with increased salivary  
110 cortisol stress responses in infants at 3 months [19] and a flattened cortisol recovery slope  
111 following stress in adolescents [29], suggesting methylation of *NR3CI* may impair negative  
112 feedback of the HPA axis.

113 In the first study to examine the interplay between prenatal and postnatal depression in  
114 relation to *NR3CI* gene methylation, we showed that the association between postnatal  
115 maternal depression and *NR3CI* 1-F promoter methylation in children was stronger where  
116 mothers had reported lower depression during pregnancy, in line with the PAR hypothesis [30].  
117 However, we did not examine for sex differences. Sex differences in glucocorticoid  
118 mechanisms associated with prenatal stress have been shown in animal models. In rats, many

119 effects of prenatal stress on later development are seen only in females, and these are abolished  
120 by adrenalectomy [31]. The effects predicted by a combination of the T-W and PAR  
121 hypotheses, have been demonstrated in starlings where mismatched pre-hatch-post-hatch  
122 conditions had a greater effect on corticosterone levels in female than male chicks, but prenatal  
123 risk increased mortality in male chicks [32, 33]. In humans, a sex difference in associations  
124 between prenatal depression and *NR3C1* 1-F promoter methylation has been reported [34],  
125 although the interplay with postnatal depression however was not analysed.

126 In this study we examined predictions based on the T-W sex-biased parental investment  
127 and PAR hypotheses. In females, where individual and species vulnerability are reduced by  
128 matching environments but increased by mismatching, the presence of good prenatal  
129 conditions followed by adverse rearing experiences, and *vice versa*, will create vulnerability to  
130 child anxiety and depression. Based on the animal models, we predicted this effect in females  
131 will involve altered HPA axis reactivity arising from epigenetic modifications of the GR gene.  
132 In males, where individuals are sacrificed for species advantage, the presence of prenatal stress  
133 will create vulnerability, unmodified by later environment quality. The animal models suggest  
134 that glucocorticoid mechanisms are implicated in excess male deaths under unfavourable  
135 maternal conditions, but they may not contribute to effects of prenatal stress on functioning  
136 after birth.

137 These predictions were tested in a longitudinal study using measures of prenatal and  
138 postnatal depression, of *NR3C1* 1-F promoter region methylation at 14 months of age, and  
139 anxious depressed symptoms in children across the preschool period. We predicted that in girls  
140 but not boys, low prenatal depression followed by high postnatal maternal depression, and high  
141 prenatal depression followed by low postnatal depression will be associated with elevated  
142 anxious depressed symptoms and elevated *NR3C1* methylation which will mediate the  
143 association between mismatched maternal depression and child anxious depressed symptoms.



144 In boys, prenatal and postnatal depression will be independent risks for elevated anxious-  
145 depressed symptoms, without the interaction between them predicted for females.

146 **Materials and Methods**

147 *Design*

148 The participants were members of the Wirral Child Health and Development Study, a  
149 prospective epidemiological longitudinal cohort of first-time mothers recruited in pregnancy  
150 to study prenatal and infancy origins of emotional and behavioural disorders. The full cohort  
151 of 1233 mothers with live singleton births have participated in several waves of assessment  
152 with a stratified random sub-sample of 316 identified for additional, more intensive assessment  
153 (intensive sample). Strata were defined on the basis of low, medium and high psychosocial  
154 risk (scores of  $\leq 2$ , 3 or  $> 3$  on an inter-partner psychological abuse scale provided on entry to  
155 the study at 20 weeks of pregnancy), with higher selection probabilities for those at higher risk.  
156 Appropriately analysed, the design allows estimates of means and coefficients for the whole  
157 general population cohort to be derived even for measures available only in the intensive  
158 sample [35].

159 Approval for the procedures was obtained from the Cheshire North and West Research  
160 Ethics Committee (UK) (reference no. 05/Q1506/107). The extensive sample was identified  
161 from consecutive first-time mothers who booked for antenatal care at 12 weeks gestation  
162 between 12/02/2007 and 29/10/2008. The booking clinic was administered by the Wirral  
163 University Teaching Hospital which was the sole provider of universal prenatal care on the  
164 Wirral Peninsula. Socioeconomic conditions on the Wirral range between the deprived inner  
165 city and affluent suburbs, but with few from ethnic minorities. The study was introduced to the  
166 women by clinic midwives who asked for their agreement to be approached by study research  
167 midwives when they attended for ultrasound scanning at 20 weeks gestation. After complete  
168 description of the study to the women, written informed consent was obtained by the study  
169 midwives, who then administered questionnaires and an interview in the clinic.

170 *Participants*

171 Of those approached by study midwives, 68.4% gave consent and completed the measures,  
172 yielding an extensive sample of 1233 mothers with surviving singleton babies. The sampling  
173 flow chart has been published previously [35]. The mean age at recruitment of extensive sample  
174 participants was 26.8 years (s.d.5.8, range 18-51). Using the UK Index of Multiple Deprivation  
175 (IMD) [36] based on data collected from the UK Census in 2001, 36.6 % of the extensive  
176 sample reported socioeconomic profiles found in the most deprived UK quintile, consistent  
177 with the high levels of deprivation in some parts of the Wirral. Forty-eight women (3.9%)  
178 described themselves as other than White British.

179 In addition to assessments of the mothers at 20 weeks gestation, mothers and infants  
180 provided data at birth and postnatally at 5, 9, and 29 weeks, and at 14.19, s.d. 1.71 months ('14  
181 months'), 30.86, s.d. 2.31 months ('2.5 years'), 41.90 s.d. 2.48 months ('3.5 years') and 58.64  
182 s.d. 3.74 months ('5 years'). Two hundred and sixty-eight mothers and infants came into the  
183 lab at 14 months for detailed observational, interview and physiological measures. This was  
184 the first occasion at which saliva for DNA was collected. Seven parents declined consent for  
185 DNA collection, 3 samples were spoilt, and 25 assessments were curtailed before saliva  
186 collection because of time constraints. Sufficient DNA for methylation analyses was obtained  
187 from 181 infants. Maternal reports of child anxious-depressed symptoms were available on 253  
188 of the intensive sub-cohort at 2.5 years, on 825 of the whole cohort at 3.5 years and on 768 of  
189 the whole cohort at 4.5 years.

## 190 *Measures*

191 *Maternal depression.* Maternal symptoms of depression were assessed at 20 weeks gestation  
192 and at every follow up point using the Edinburgh Postnatal Depression Scale (EPDS), which  
193 has been used extensively to assess prenatal and postnatal depression [37].

194 *DNA methylation.* Methylation status in the *NR3C1* 1-F promoter was examined at the same  
195 CpGs (CpG unit 22 and 23, shown in Figure 1) identified in previous studies (24). DNA  
196 collected from Oragene® saliva samples, was extracted, bisulphite treated, amplified (Forward,  
197 GACCTGGTCTCTCTGGGG; Reverse, TGCAACCCCGTAGCCCCTTTC) and run on a  
198 Sequenom EpiTYPER system (Sequenom Inc., San Diego, US), providing an average for  
199 methylation across the two CpG units. Data was transformed to percentage of methylation at  
200 CpG unit 22 and 23 to allow for comparison with previous analysis of differential methylation  
201 at this locus.

202 FIGURE 1 ABOUT HERE

203 *Child anxious-depressed symptoms.* Child symptoms were assessed by maternal report at 2.5,  
204 3.5 and 5.0 years using the preschool Child Behavior Checklist (CBCL) [38]. It has 99 items  
205 each scored 0 (not true), 1 (somewhat or sometimes true), and 2 (very true or often true), which  
206 are summed to create seven syndrome scales. Only the anxious/depressed scale was analysed  
207 for this report, and as recommended in the CBCL manual, raw scores were used [39].

208 *Stratification variable and confounders .* Partner psychological abuse was assessed using a 20  
209 item questionnaire covering humiliating, demeaning or threatening utterances in the partner  
210 relationship during pregnancy over the previous year [40]. Maternal age (at this first  
211 pregnancy), marital status at 20 weeks gestation, and socioeconomic status were included as  
212 covariates because of their established associations with adult depression. Socioeconomic  
213 status was determined using the revised English Index of Multiple Deprivation (IMD) [36]  
214 based on neighborhood deprivation. All mothers were given IMD ranks according to the  
215 postcode of the area where they lived and assigned to a quintile, based on the UK distribution  
216 of deprivation. Mother's years of education at enrolment in the study was recorded. Information  
217 about smoking was obtained at 20 and 32 weeks gestation and was included because of

218 published associations with altered DNA methylation [41]. Birth records provided sex of  
219 infant, one-minute Apgar score, and birth weight and gestational age, from which a measure of  
220 fetal growth was obtained. Low fetal growth is associated with elevated fetal glucocorticoid  
221 exposure and so might be associated with elevated *NR3C1* gene methylation. Obstetric risk  
222 was rated using a weighted severity scale developed by a collaboration of American and Danish  
223 obstetricians and paediatric neurologists [42].

#### 224 *Statistical Analysis*

225 All analyses were undertaken in Stata 14 (StataCorp, 2015). Generalised structural  
226 equation models (SEM) were fitted using the `sem` procedure and estimated by maximum  
227 likelihood to allow inclusion of participants from both intensive and extensive strata. The  
228 anxiety-depression scores at 2.5, 3.5 and 5.0 years and *NR3C1* percent methylation at 14  
229 months were highly skewed so scores were log-transformed and Winsorized at 2.5 standard  
230 deviations to reduce their skew. For further robustness, we report standard errors and p-values  
231 based on the heteroscedastic consistent estimator of the parameter covariance matrix. The  
232 main analyses included the stratification variable and confounds except for perinatal confounds  
233 as they may lie on a mediational pathway from prenatal depression, however the effect of  
234 adding those variables was examined. Model estimates and tests allowed for differential  
235 missingness associated with any of the covariates and observed responses included in the  
236 model, accounting for the stratified study design.

237 The pre-post environment mismatch predictions on both methylation and child symptoms  
238 were examined first by testing for two-way interactions between prenatal and postnatal  
239 depression in models estimated separately in females and males. We then tested for the sex  
240 difference by examining the three-way, sex by prenatal depression by postnatal depression  
241 interactions in a model that included both genders. The effects of combinations of prenatal and

242 postnatal depression giving rise to these interaction effects are shown in the figures. The  
243 prediction of additive effects of prenatal and postnatal depression in boys was examined in  
244 models without interaction terms.

245         In the fitted models methylation was specified as a factor, measured without error by the  
246 observed methylation, a device that implicitly imputes rates of methylation where these have  
247 not been observed, but doing so in a manner which recognises our uncertainty in these  
248 unobserved values. This enables participants with partial data that would be informative for  
249 some parts of the model to be included.

250 **Results**

251 Table 1 gives summary statistics for males and females separately for the measures  
252 included in the analysis and shows the sample size at each data collection point. As described  
253 in the statistical analysis section, differences in the available sample for different measures  
254 were accounted for by use of weighted, maximum likelihood or covariate adjusted estimators.  
255 Figure 2 shows the structure of the SEM model in which maternal history of depression predicts  
256 *NR3C1* methylation (solid red arrows) and maternal report of child anxious-depressed  
257 symptoms (solid black arrows). These analyses included the 412 girls and 382 boys on whom  
258 there were measures of maternal depression and maternal report of child anxious-depressed  
259 symptoms at a minimum of one follow up point as well as all confounders.

260 FIGURE 2 ABOUT HERE

261

262 Table 1 Summary statistics for outcomes, predictors and variables included as potential  
 263 confounders for the modelled sample (I = measure based on intensively assessed sub-sample  
 264 only)

	Girls			Boys		
	N	Mean	SD	N	Mean	SD
Child anxious-depressed symptoms 2.5 years(I)	125	1.54	1.77	120	1.27	1.61
Child anxious-depressed symptoms 3.5 years	387	1.60	1.64	366	1.59	1.70
Child anxious-depressed symptoms 5 years	372	1.76	1.96	347	1.78	2.01
Child <i>NR3C1</i> methylation(I)	89	3.42	1.85	87	3.55	1.96
Prenatal EPDS maternal depression scores	412	6.94	4.74	382	7.42	4.54
Mean postnatal EPDS maternal depression scores	412	5.24	3.92	382	5.79	4.35
Stratum low	412	77%		382	75%	
Stratum mid		8%			7%	
Stratum high		16%			18%	
Maternal age <21 years	412	10%		382	12%	
Maternal age 21-30 years		56%			56%	
Maternal age >30 years		34%			32%	
No maternal education beyond age 18	412	62%		382	67%	
Smoking – none	412	62%		382	64%	
Smoking before pregnancy		21%			19%	
Smoking during pregnancy		17%			18%	
No partner	412	17%		382	19%	
Most Deprived Quintile	412	37%		382	36%	
Obstetric risk index	412	2.20	1.18	382	2.20	1.19
Birthweight/gestation (gm/wk)	412	83.6	11.9	382	86.5	11.4
1 Minute Apgar score	412	8.95	1.60	382	8.86	1.76

265



266 Table 2 shows for girls and boys separately the estimated path coefficients from the  
267 standardised prenatal depression, postnatal depression and their interaction (product) of  
268 primary interest accounting for the stratification, attrition and confounders. We first tested the  
269 prediction that there would be an interaction between prenatal and postnatal depression in girls  
270 but not in boys. In girls there was a significant effect of the interaction between prenatal and  
271 postnatal depression on both child anxiety-depression ( $p=.011$ ) and *NR3C1* 1-F promoter  
272 methylation ( $p<.001$ ). For boys, by contrast, anxious-depressed symptoms were not predicted  
273 by the prenatal and postnatal depression interaction term ( $p=.920$ ), and the effect on *NR3C1*  
274 methylation was smaller than for girls, though still significant ( $p=.003$ ). Adding the three  
275 additional potential confounders that were assessed after the prenatal exposure (obstetric risk  
276 index, 1-minute Apgar score and birthweight/gestational age) made no material difference to  
277 these associations. Fitting this model to boys and girls together, but allowing the effects of  
278 prenatal and postnatal depression exposure on the two correlated outcomes to differ by sex (in  
279 addition to a gender main effect), a Wald test of the sex differences in the effect of the prenatal-  
280 postnatal depression interaction on both outcomes (a difference of 0.20 for anxiety-depression  
281 and 0.18 for methylation) gave  $\chi^2(2)$  of 5.95 ( $p=.051$ ), with the two individual interactions  
282 contributing equally (anxiety-depression  $p=.088$ , methylation  $p=.069$ ).

283

284 Table 2 Summary of SEM analyses predicting *NR3C1* 1-F promoter methylation and child  
 285 anxious depressed symptoms  
 286

	Female (n=412)		Male (n=382)	
	Std Coeff [p-value]	95% C.I	Std Coeff [p-value]	95% C.I
Effects on child anxious-depressed symptoms				
Prenatal maternal depression	-0.06	-0.23, 0.11	0.16	-0.00, 0.33
Postnatal maternal depression	0.21	0.05, 0.38	0.17	0.03, 0.31
Prenatal-postnatal interaction	-0.19 [p=.011]	-0.34,-0.05	0.01 [p=.920]	-0.11, 0.12
Effects on child <i>NR3C1</i> 1-F promoter methylation				
Prenatal maternal depression	-.02	-0.28, 0.24	-0.11	-0.34, 0.12
Postnatal maternal depression	0.45	0.16, 0.75	0.38	0.11, 0.65
Prenatal-postnatal interaction	-0.39 [p=.00001]	-0.56, -0.21	-0.21 [p=.003]	-0.32. -0.08
Child anxious-depressed symptoms factor loadings				
2.5 years	0.81		0.72	
3.5 years	0.80		0.67	
5 years	0.57		0.81	
Model fit				
	RMSEA = .05 (95% C.I. .03-.07) CFI = .90		RMSEA = .01 (95% C.I. .01-.04). CFI = 1.00	

287

288 **Legend.** The table shows standardized factor loadings of child CBCL anxious-depressed  
 289 symptoms at ages 2.5, 3.5 and 5 years, and main effects and effects of interaction of prenatal  
 290 and postnatal depression in the prediction of the anxious-depressed factor and the *NR3C1* 1-F

291 promoter methylation (effects of stratification factors and confounders not shown). Anxious-  
292 depressed symptoms and methylation are analysed together as correlated outcomes in an  
293 SEM. Coefficients for the effects of confounders and stratification factors are not shown  
294 (stratum, maternal age, maternal smoking, maternal education, no partner, neighbourhood  
295 deprivation). The models reported used robust standard errors to guard against inferential  
296 errors due to non-normality. In order to provide conventional model fit statistics the models  
297 were run without robust standard errors and the statistics from this reported in the final row of  
298 the table.

299

300

301 We then tested the prediction that in boys there would be independent and additive effects  
302 of prenatal and postnatal depression, by estimating the model (not shown in the Table) for boys  
303 without the interaction term. This showed a significant effect on child anxiety-depression of  
304 postnatal depression (standardised coefficient 0.17, CI 0.04 to 0.30,  $p = .011$ ) and an effect of  
305 similar magnitude, that was non-significant, of prenatal depression (0.15, CI -0.02 to 0.33,  
306  $p=.080$ ). Independent effects on methylation were not seen (prenatal 0.05, CI -0.17 to 0.27,  
307  $p=.640$ ; postnatal 0.13, CI -0.09 to 0.36,  $p=.241$ ).

308 Figure 3 displays how the interactions between prenatal and postnatal depression in the  
309 prediction of anxious-depressed symptoms differed between girls and boys. It can be seen that  
310 in girls, at a low level of prenatal depression (1 standard deviation below the mean), increasing  
311 postnatal depression was strongly associated with increasing child anxious-depressed  
312 symptoms, while at a high level there was no association. With prenatal depression at the mean,  
313 the association was intermediate between the low and high prenatal levels. In boys, by contrast,  
314 as evidenced in parallel regression lines, there was no interplay between prenatal and postnatal  
315 maternal depression.

316 FIGURE 3 ABOUT HERE

317 As shown in Figure 4, the effects of prenatal-postnatal mismatch on methylation were  
318 again strongly evident in girls, with the greatest association between postnatal depression and  
319 methylation in the presence of low prenatal depression, and progressively weaker associations  
320 at higher levels of prenatal depression. The progressive effect of prenatal depression was also  
321 evident in boys but was less strong.

322 FIGURE 4 ABOUT HERE

323

324 In girls, replacing the correlation between the methylation and anxiety-depression factors  
325 by a causal effect, higher *NR3C1* methylation at 14 months was associated with higher anxiety-  
326 depressed symptoms (standardised coefficient 0.36 CI 0.05 to 0.67,  $p=.025$ ), illustrated in the  
327 left hand panel of Figure 5. The residual direct effect of the prenatal-postnatal interaction on  
328 child anxiety-depression symptoms was substantially reduced, from -0.19 (shown in Table 2)  
329 to -0.06 (CI -0.26 to 0.15), becoming wholly nonsignificant ( $p=.600$ ). For boys there was no  
330 evidence of an effect of methylation on symptoms (standardised coefficient -0.03, CI -0.31 to  
331 0.24,  $p=.820$ ).

332

FIGURE 5 ABOUT HERE

## Discussion

333

334 Many, although not all, of our predictions based on the evolutionary T-W and PAR hypotheses  
335 for sex-biased parental investment and fetal programming were supported in this longitudinal  
336 study, from 20 weeks of pregnancy and over the first 5 years of children's lives. Mismatching  
337 between prenatal and postnatal maternal depression was associated with greater anxious-  
338 depressed symptoms and *NR3C1* methylation in girls. Both effects were most evident in girls  
339 exposed to high levels of postnatal depression. Their symptoms and *NR3C1* methylation were  
340 higher where their mothers had reported low levels of depression during pregnancy, in line  
341 with the idea that they had not been prepared by the fetal environment for postnatal exposure  
342 to maternal depression. In girls only, elevated *NR3C1* was associated with higher anxious-  
343 depressed symptoms and mediated the association between maternal depression and child  
344 symptoms. In boys, there was no evidence of effects of prenatal – postnatal depression  
345 mismatch on anxious-depressed symptoms. However, and contrary to our prediction, the  
346 prenatal-postnatal mismatch effect on *NR3C1* methylation was seen in boys as well as in girls,  
347 although the size of the effect was smaller.

348 The strengths of the investigation include a prospective study with a general population  
349 sample, accounting for a number of plausible confounds and factors associated with attrition.  
350 Also, by using SEM to create a latent variable from measurement at 3 time points over 2.5  
351 years, we reduced the risks arising from multiple testing for each time point, and we were able  
352 to examine the predictions in relation to persistently elevated symptoms likely to confer risk  
353 for an elevated trajectory for anxious-depressed symptoms over childhood [43]. The method  
354 adopted for missing methylation data exploited the properties of maximum likelihood for  
355 accounting for data assumed missing at random. Most missingness was by design because of  
356 the systematic stratification of the intensive sample, thus meeting this assumption, and  
357 inclusion of multiple covariates allowed us account for unplanned attrition. It is nevertheless

358 possible that not all the necessary confounds to deal with non-random missingness were  
359 identified.

360 There were four principal limitations in relation to the measurement of *NR3CI*  
361 methylation. First, peripheral cell samples, both from blood and saliva, are heterogeneous,  
362 which may account for some of the variability in methylation. This can introduce a confound  
363 where other variables are associated with cellular heterogeneity [44]. Second, while studies  
364 combining peripheral cell and CNS post mortem estimations suggest that they are often  
365 substantially correlated [45], it cannot be assumed that DNA methylation in peripheral tissues  
366 reflects methylation in relevant CNS regions. This is particularly a concern because of  
367 substantial variations in epigenetic effects across brain regions and cell types. Specifically, it  
368 cannot be assumed that variations in the *NR3CI* 1-F promoter in saliva reflect variations in  
369 glucocorticoid receptor synthesis in the hippocampal regions involved in HPA axis regulation.  
370 Third DNA methylation is one of a number of an epigenetic processes that regulate gene  
371 expression, and so does not provide a direct measure of that expression. ‘Mediation’ in this  
372 report, as in the field more widely [46], refers to statistical findings consistent with, but not  
373 direct evidence of, epigenetic mediation. Fourth, there are many combinations of CpG sites,  
374 even on a relatively circumscribed region such as the *NR3CI* 1-F promoter that could be  
375 examined, leading to the risk of multiple analyses and ‘significant’ findings occurring by  
376 chance. Fifth, although we accounted for several plausible confounds, environmental variables  
377 other than those included in analyses may better account for the findings.

378 No one study can establish the validity of estimates of peripheral cell methylation as  
379 indices of CNS methylation, however a finding of the same pattern of associations for  
380 peripheral cell methylation and for behaviours that undoubtedly reflect CNS function, and for  
381 mediation of the association between maternal depression and symptoms by *NR3CI*  
382 methylation is relevant to the issue. As is evident from the SEM models, and as seen in Figures

383 3 and 4, there were striking similarities between the patterns of associations involving  
384 interactions between prenatal and postnatal depression and sex differences, not only for child  
385 anxious-depressed symptom but also for *NR3C1* methylation. Furthermore, in this study we  
386 reduced risks arising from multiple analyses of many potential methylation sites by examining  
387 only one site that had been identified from a meta-analysis of previous studies [24].



## 388 **Conclusions**

389 Our findings are important in five major ways. First, they provide pointers to study  
390 designs that could be introduced into animal models where mechanisms can be examined using  
391 experimentally controlled risks. These would, for example, examine the interplay between  
392 prenatal and postnatal risks in relation to the role of the placenta in regulating passage of  
393 maternal glucocorticoids to the foetus, which in turn can be controlled by further epigenetic  
394 modifications of specific placental genes [47]. Second, they illustrate how evolutionary  
395 hypotheses regarding parental investment in offspring can be used to generate novel, and in  
396 some ways surprising, predictions regarding parenting and early development in humans [48].  
397 Third, testing in this way can generate further productive questions. In this study, while there  
398 was good evidence for mismatch effects in females on *NR3CI* methylation and child  
399 symptoms, and for a sex difference in relation to child symptoms, the prenatal-postnatal  
400 depression mismatch was also associated with *NR3CI* methylation in males, which was  
401 contrary to the predictions. Further study is needed into the conditions under which fetal  
402 programming effects are seen in males as well as females, and under what conditions there are  
403 sex differences in the behavioural implications of *NR3CI* methylation. Fourth they show that,  
404 even though human development is subject to many complex social and psychological  
405 influences, biological mechanisms conserved across many non-human species, can be highly  
406 influential. Fifth they suggest that some prenatal effects on epigenetic and behavioural  
407 outcomes in early childhood, differ radically in males and females, and so further study of sex  
408 specific mechanisms is needed. This will have implications for our understanding of the  
409 biology of psychiatric disorders arising in childhood.

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419

420 **Authors' contributions**

421 JH, HS, AP designed the study, CM, JQ conducted the methylation estimations, JH, HS, NW  
422 supervised data collection, JH, AP, NW analysed the data, JH, AP, HS, NW wrote the paper,  
423 and all authors read and approved the final manuscript.

424

425 **Conflict of interests**

426 None of the authors has a conflict of interest.

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